Remarks

Status of the claims

Prior to entry of this amendment claims 40-54, 56-62 and 64-66 are pending in this application, of which claims 41, 53, 54, 59, 60, 64, and 65 are withdrawn by the Office. Claims 40-42, 48, 51, 56, 61, and 66 are amended herein. Claims 57-60, and 62 are canceled and new claims 66-76 are added. Unless specifically stated otherwise, none of these amendments is intended to limit the scope of any claim. Applicants reserve the right to prosecute any deleted or withdrawn subject matter in a related application.

Support for the amendment of claims 40 and 51 can be found throughout the specification and at least at page 66, line 5 through page 67, line 15. Claims 41 and 42 are amended for antecedent basis. Claim 48 is amended to correct an obvious clerical error. Support for the amendment of claim 56 and new claim 73 can be found throughout the specification and at least at page 64, line 16 through page 65, line 10. Claim 61 is amended to correct dependency. Support for the amendment of claim 66 and new claims 67 and 74 can be found on page 63, line 20-24. Support for new claims 68-72 can be found throughout the specification and original claims 40-50. Support for new claims 75 and 76 can be found throughout the specification and specifically page 63, line 20 through 66, line 2

After entry of this amendment claims 40-54, 56, 61, and 64-76 are pending, of which claims 41, 53, 54, 64, and 65 are withdrawn by the Office as drawn to non-elected species. Applicants request that the non-elected species be rejoined when the generic claims are allowed. Applicants believe no new matter is added herein. Reconsideration of the rejected claims is requested.

Information Disclosure Statements

Applicants thank the Examiner for considering the references cited in the IDSs filed March 31, 2005, January 3, 2008, and September 18, 2007. Applicants note however that the supplemental IDS form PTO-1449 submitted December 14, 2005, has not been initialed by the Examiner to document that the references cited therein were considered by the Examiner.

Applicants believe that this is simply a clerical error, as the second page of this form includes the Examiner's signature and indicates that the IDS was considered on May 5, 2008. To ensure that the record is clear, Applicants have provided an additional copy of the PTO-1449 form submitted on December 14, 2005. Applicants respectfully request that the Examiner initial and date this copy of the PTO-1449 to make the record clear that the listed references were considered.

Documents Submitted Herewith

Presented herewith in support of the Applicants' arguments are three journal articles (Exhibit A, Exhibit B and Exhibit C). The following brief descriptions are provided to give context.

Exhibit A

Exhibit A is a post filing date publication (Zhu *et al.*, Molecular and Cellular Biology 26(24): 9279-9290, 2006) demonstrating that a reduction in nucleostemin levels induces senescence *in vivo*. The manuscript describes experiments in which a reduction in nucleostemin levels in heterozygous null nucleostemin mice lead to an increase in the numbers of senescent cells (see e.g. page 9281 second column, second full paragraph). This article demonstrates that modulation of nucleostemin levels increases senescence *in vivo*.

Exhibit B

Exhibit B is post filing date publication (Jafarnejad *et al.*, Cell Proliferation 41: 28-35, 2008) demonstrating that over expression of nucleostemin increases senescence. The manuscript describes experiments in which misexpression of nucleostemin (both increased and decreased) induced senescence of rat derived bone marrow stromal cells (see e.g. page 32). This article demonstrates that altered expression of nucleostemin increases cellular senescence in cells in addition to osteocarcinoma cells and CNS stem cells.

Exhibit C

Exhibit C is post filing date publication (Dia *et al.*, Molecular and Cellular Biology 28(13): 4365-4376, 2008) demonstrating that over expression of nucleostemin increases senescence. The manuscript describes experiments in which overexpression of nucleostemin

(*i.e.* increased levels of nucleostemin) induced senescence of U2OS cells (see e.g. page 4369 second column, first full paragraph). This article demonstrates that over expression of nucloestemin increases cellular senescence.

Claim rejections

Rejections under 35 USC §112, first paragraph (Written Description)

Agents that alter the level of nucleostemin

Claims 40, 43,-51, 56-58, and 62 are rejected for alleged failure to comply with the written description requirement. Specifically the Office contends that the specification does not provide descriptive support for the full genus of agents that alter the level of nucleostemin.

The Office is reminded that as stated in M.P.E.P. 2163(1)(A) "Written Description:" "[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims")."

Possession of a genus may be satisfied through sufficient description of a "representative number of species" by: (a) an actual reduction to practice, (b) a reduction to drawings, or (c) disclosure of relevant, identifying characteristics, for example structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. In other words, possession of a genus can be evidenced by describing the distinguishing identifying characteristics common to the divergent species encompassed. In this case the identifying characteristic is that the agent is identified as one that alters the level of nucleostemin.

The specification provides actual reduction to practice of several members of the genus of agents that alter the level of nucleostemin, including nucleic acids encoding nucleostemin and siRNAs. The specification also discloses several other members of the genus of agents that can alter the level of nucleostemin, including a nucleostemin polypeptide (page 47, line 2); an antisense molecule (page 49, line 22 and page 50, line 31 through page 51 line 15), ribozyme that specifically binds nucleostemin (page 49, line 23 and page 50, lines 17-30). Given that the

specification describes, several member of the genus of agents encompassed by the claims, Applicants respectfully submit that they have met their written description burden. Specifically, the examples identified are sufficiently representative of the variation found within the claimed genus such that one of skill in the art would recognize that Applicants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Applicants request that the rejection of the claims 40, 43,-51, 56-58, and 62 under 35 U.S.C. § 112, first paragraph be withdrawn in view of the amendments and remarks made herein.

Nucleostemin targets with 95% identity to SEQ ID NO: 10

The Office contends that the specification does not provide adequate written description for nucleostemin peptides with at least 80% sequence identity to SEQ ID NO: 6. Applicants respectfully disagree with this rejection. However, solely to advance prosecution Applicants have amended claim 40 to specify that the nucleostemin peptides are at least 95% identical to SEQ ID NO: 10. Claim 51 has been amended to specify that the nucleostemin peptides are at least 95% identical to SEQ ID NO: 6. To the extent the rejection might be applied to the amended claims, Applicants respectfully traverse this rejection. At issue here is whether one of ordinary skill in art would recognize a species other than those exemplified in the specification, but within the broad generic claim. Applicants assert that the recitation of at least 95% sequence identity provides a very predictable structure for the sequences employed in the claims for at least the reasons stated below.

The amino acid sequence of SEQ ID NO: 10 is provided in the specification and those of skill in the art could readily envision all of the amino acid sequences that share at least 95% sequence identity to a polypeptide encoded by the nucleotide sequence of SEQ ID NO: 10. The specification contains several examples of sequences that have at least 95% sequence identity to SEQ ID NO: 10, including SEQ ID NO: 2, SEQ ID NO: 4, and SEQ ID NO: 6. Furthermore, the specification at least in Example 2 (page 60) teaches which residues are likely to be conserved amongst nucloestemin variants, such that the one of ordinary skill in the art would recognize a nucleostemin from a simple sequence comparison. For example the specification describes PROSITE analysis and Conserved Domain search identified two consensus motifs that define GTP-binding proteins (the G4 motif KXDL and the the G1 or P-loop GXXXXGK(S/T). PSORT analysis revealed multiple nuclear localization sequences and a coiled-coil domain (FIGS. 1C,

1D). Thus one of ordinary skill would have known (at the time of filing) what residues of nucleostemin encoded by either SEQ ID NO: 10 or SEQ ID NO: 6 could or should not be varied while still preserving function, based on shared homology to a known family of functional proteins and conservation of that protein family's conserved residues. Thus, Applicants submit that the knowledge and level of skill in the art at the time of Applicants' filing would allow a person of ordinary skill to envision the entire scope of the claimed invention, for altering the level of a nucloestemin peptide that is at least 95% identical to SEQ ID NO: 10 or 6. Applicants request that the written description rejection under 35 U.S.C. §112, first paragraph be withdrawn.

Rejections under 35 USC §112, first paragraph (Enablement)

Claims 40, 42-52, 56-58, 61, 62, and 66 are rejected under 35 U.S.C. §112 first paragraph for alleged lack of enablement. Specifically, the Office contends that enablement is only provided for inducing senescence in CNS stem cells and U2OS cells by the *in vitro* administration of a siRNA targeting nucleostemin. The Office further contends that enablement is not provided for inducing senescence *in vivo* by any means. Applicant respectfully disagrees and submits that, in view of the amendments and arguments made herein, the claims are enabled and undue experimentation is not required to practice the invention as claimed.

The test of enablement is whether one reasonably skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. In this case, the Office asserts that the scope of enablement is limited to the disclosed species and examples. However, to provide effective incentives, claims must adequately protect inventors. "To demand that the first to disclose limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts." *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976). Furthermore, the instruction to interpret claims in light of the specification "does not mean that everything in the specification must be read into the claims." *Raytheon Co. v. Roper Corp.,* 724 F.2d 951, 957, 220 USPQ 592, 597 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 835 (1984).

A specification is presumed to be in compliance with the enablement requirement of 35 U.S.C.§ 112, first paragraph. Accordingly, the burden is on the Patent Office to establish a reasonable basis to question enablement. In this case, it appears that the Office is holding the application to a higher standard than is warranted by the statute, the guidelines and the relevant case law. As noted above, it is well established that a specification need not explicitly describe every aspect of every embodiment encompassed by the claims. The first paragraph of 35 U.S.C. § 112 requires nothing more than objective enablement and not the extraordinary level of detail and predictability the Office demands. For this reason the rejection of claims 40, 42-52, 56-58, 61, 62, and 66 under 35 U.S.C. § 112, first paragraph is fundamentally flawed and Applicants request that this rejection be withdrawn.

Inducing Senescence in Different Cell Types

It is well established that a specification need not explicitly describe every aspect of every embodiment encompassed by the claims. An Applicant preferably omits from a patent specification description that which is well known in the art (see M.P.E.P. § 2164.01). The emphasis in the test for enablement is on "undue," and not on "experimentation" (see *In re Wands*, 858 F.2d 731, 736-40 (Fed. Cir. 1988)). A considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance in which the experimentation should proceed. *Id.* The determination of what is meant by "undue experimentation" has been characterized by the Federal Circuit as follows (*Genentech, Inc.* v. *Novo Nordisk A/S*, 108 F.3d at 1365):

> [t]he test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention.

In the current case, any necessary experimentation to test induced senescence in various cell types is merely routine, and thus not undue. It is believed that any testing is well within the limits set by the *Genentech* court.

Applicants respectfully submit that, although routine testing may be required in order to identify cell types where senescence can be induced by modulation of nucleostemin levels, such testing would not be considered undue. The present application provides the guidance necessary to identify such cell types. For example the specification describes in Example 9 (page 66) methods of identifying induced senescence in a cell. Furthermore methods of isolating different cell types are routine in the art. Therefore, undue experimentation is not required to identify cell types where senescence can be induced by modulation of nucleostemin levels. For example the post filing date journal articles submitted herewith (Exhibit A and Exhibit B) describe the identification of other cell types for which modulation of nucleostemin induces cell senescence. For example Exhibit A describes induced senescence *in vivo* using a nucleostemin mouse knock out model. In a specific example, induced senescence was detected in mouse embryonic fibroblasts with reduced nucleostemin (see page 9281, second full paragraph). Exhibit B describes induced senescence in bone marrow stromal cells from either an increase or decrease in nucleostemin levels (see *e.g.* page 32). There are therefore multiple examples described in the specification and the publications provide herewith describing the vast array of cell types that can be induced to undergo senescence by alteration of nucleostemin levels. Given the guidance and teaching present in the specification as well as the knowledge readily available, it is well within the skill of one of ordinary skill in the art to practice the full breadth of the invention as claimed, namely the induction of senescence in a cell by administration of an agent identified as one that alters the level of nucleostemin.

Senescence Induced in Vivo

The Office contends that the specification is not enabled for *in vivo* induced senescence. Applicants respectfully disagree and present herewith Exhibit A, a journal article demonstrating that modulation of nucleostemin levels *in vivo* induces senescence. This journal article (authored by one of the inventors) shows in a mouse knockout model of nucleostemin, that senescence can be induced *in vivo* by a reduction of nucleostemin. This post filing date publication demonstrates that senescence is induced *in vivo* by altering the level of nucleostemin in a cell *in vivo*. Therefore, claims to methods of inducing senescence by the *in vivo* are enabled by the disclosure in the specification.

siRNA Therapy

As to enablement of siRNA therapy, the Office's generalized challenge to enablement would seemingly apply to any claim that encompasses siRNA compositions and therapies. Accordingly, it appears that the Office finds the entire field of siRNA therapy to be fundamentally and irredeemably unpredictable. In fact, from the context of the rejection, one would presume that an Applicant could never obtain protection for a claim that encompasses siRNA therapy without both conclusive clinical trial data and extensive detail regarding administration parameters and even then one would be restricted to the specifics of the embodiments actually tested. This is clearly both unreasonable and in conflict with the statute, the rules and the guidelines of the USPTO as set forth in the M.P.E.P. Furthermore, as is well established by current case law, Applicants need not prove clinical efficacy to show that a therapeutic process is operable (*i.e.*, enabled). As stated in M.P.E.P. § 2107.01, the "courts have found utility for therapeutic inventions, despite the fact that an applicant is at a very early stage in the development of a therapeutic regimen" or that a therapeutic treatment regimen is not at a stage where it is ready to be practiced on humans. *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985); *In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Moreover, it is not within the province of the Office to require proof of efficacy in animals prior to granting a patent that encompasses therapeutic methods. In fact, the USPTO guidelines are explicit on this point stating that "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility [*i.e.*, operability & enablement] for an invention related to treatment of human disorders" (M.P.E.P. § 2107.03). The guidelines further state that "[t]he Office must confine its review of patent applications to the statutory requirements of the patent law, and in quoting *In re Brana*, *supra*, that "FDA approval, however, is not a prerequisite". *Id.*

For the reasons given above, Applicants respectfully submit that the scope of the pending claims is commensurate with the specification's scope of enablement. In view of the amendments and arguments made herein. Applicants submit that the claims currently pending

are fully enabled by the specification. Applicants request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Prior art rejections

The Office has rejected claims 40, 42, 43, 46-51, 56-58, and 62 under 35 U.S.C. § 102(e) as allegedly anticipated by Kennedy *et al.*, (U.S. Patent Publication No 2003/0008284). The Office has rejected claims 40, 42-51, 56-58, 61, 62 and 66 under 35 U.S.C. § 103(a) as allegedly obvious over Kennedy *et al.* either alone or in combination with Bass (2001, Nature 411:428-9).

Kennedy *et al.*, discloses SEQ ID NO: 22 which is alleged to be 80% identical to SEQ ID NO: 6 (nucleostemin). Kennedy *et al.*, further discloses that the SEQ ID NO: 22 is over-expressed in colon cancer. Kennedy *et al.* does not teach or suggest that SEQ ID NO: 22 is functionally responsible for regulating senescence. In fact Kennedy *et al.* does not disclose inducing senescence or detecting senescence at all.

Bass teaches that siRNA treatment of cells is more effective than antisense at reducing expression of a target gene. Bass does not teach or suggest nucleostemin or inducing senescence or detecting senescence.

Claims 40, 42, 43, 46-50, 56, 61, 64 and 65

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The elements must be arranged as required by the claim." *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). M.P.E.P. 2131.

As amended herein claim 40 (and therefore all claims dependent therefrom) include the feature of "**determining senescence of the cell**." This feature is neither taught nor suggested by Kennedy *et al.* Kennedy *et al.* merely teaches that SEQ ID NO: 22 (more specifically the nucleic acid sequence encoding SEQ ID NO: 22) is upregulated in colon cancer. Because Kennedy *et al.* does not teach all the elements of claim 40 either implicitly or inherently, this reference cannot

anticipate claim 40 or any claims dependent therefrom (*i.e.* claims 40, 42, 43, 46-50, 56, 61, and 66).

Claim 40 (and all claims dependent therefrom) are not obvious in view of Kennedy *et al.* alone or in combination with Bass because the cited references fail to teach or suggest each and every element of claim 40, which is required for an obviousness rejection (M.P.E.P. 2143.03). As amended herein claim 40 include the recited method step of "determining senescence of the cell." As discussed above, Kennedy *et al.* does not teach inducing senesce and certainly does not teach the determining senescence. This deficiency is not overcome by Bass, which make absolutely no mention of senescence. Furthermore, one of skill in the art would not be motivated to produce the clamed invention based on the teachings of Kennedy *et al.* and/or Bass because based on the teachings present in Kennedy *et al.* there would be no expectation of success. Kennedy *et al.* in Example 8 (see numbered paragraphs [0289]-[0296]) describes the experimental results of a reduction in expression of several genes identified as over-expressed in colon cancer using antisense technology in the human colon cancer cell line SW620. The genes down regulated in this experiment include c454001 (see Table 2 page 25), which corresponds to SEQ ID NO: 22 (and SEQ ID NO: 6 of the present application). The last sentence of Example 8 (numbered paragraph [0296]) reports that only "one such use of the antisense oligonucleotides described by SEQ ID NO: 108 [which did not target c454001] resulted in inhibition of proliferation of SW620 cells." Therefore, this example teaches that a reduction of nucleostemin has no effect on cell proliferation or more importantly inducing senescence. One of ordinary skill in the art would reading Kennedy *et al.* would believe that a reduction of nucleostemin expression has no effect on a cell. Therefore there would be no expectation that a modification of Kennedy *et al.* would be successful in producing the claimed invention. For at least this reason there is no *prima facie* case of obviousness with respect to claim 40 or any claims dependent therefrom (*i.e.* claims 40, 42, 43, 46-50, 56, 61, and 66) and Applicants request that the rejections be withdrawn.

Claim 48

In addition to the reasons set forth with respect to claim 40, Kennedy *et al.* alone or in combination with Bass cannot anticipate nor render claim 48 obvious because Kennedy *et al.*

does not teach inducing senescence of a stem cell. In fact Kennedy *et al.* does not mention stem cells at all. Therefore, Kennedy *et al.* does not teach all the elements of claim 48 (namely inducing senescence of a stem cell). For this additional reason claim 48 is allowable.

Claim 51

For the reasons set forth with regard to claim 40, claim 51 is not anticipated or obvious over Kennedy *et al.* either alone or in combination with Bass. As amended herein claim 51 (and all claims dependent therefrom) include the claim feature of "measuring the senescence of the tumor cell in the subject." Kennedy *et al.* and Bass neither disclose nor suggest inducing senescence and certainly do not teach or suggest measuring senescence of a cell. For at least this reason claim 51 and all claims dependent therefrom are not anticipated or obvious over Kennedy *et al.* and Bass.

Claim 56

For the same reasons cited for claim 48, Kennedy *et al.* alone or in combination with Bass cannot anticipate nor render claim 48 obvious because Kennedy *et al.* does not teach inducing senescence of a stem cell. For this additional reason Kennedy *et al.* does not anticipate claim 56.

Claim 66

Claim 66 is amended herein to recites a siRNA consisting of the nucleic acid sequence according to SEQ ID NO: 7. Kennedy *et al.* does not teach or suggest a nucleic acid sequence consisting of SEQ ID NO: 7. Bass does not teach or suggest a nucleic acid sequence consisting of SEQ ID NO: 7. Kennedy *et al.* and Bass do not teach all of the elements of the claim and therefore claim 66 is not anticipated or obvious over Kennedy *et al.* and/or Bass.

Claim 67

New claim 67 recites a siRNA consisting of the nucleic acid sequence according to SEQ ID NO: 7. Claim 67 is allowable for the same reasons set forth for claim 66.

Claims 68-76

New claims 68-76 include features not found in the prior art of record and are thus allowable.

Dependent Claims

All rejected dependent claims depend from a rejected independent claim and are allowable for the same reasons as the corresponding independent claim. "If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)." M.P.E.P. 2143.03. Each of the dependent claims is further allowable in view of the patentable combination of features recited in such dependent claim.

Conclusion

Based on the foregoing amendments and arguments, the claims are in condition for allowance and notification to this effect is requested. The Examiner is formally requested to contact the undersigned prior to issuance of the next Office action, in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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